American Red Cross

National Headquarters

July 14, 2000

Docket Officer
Dockets Management Branch (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, MD 20852

RE: Suitability Determination for Donors of Human Cellular and Tissue Based Products [Docket No. 97N-484S, 65 FR 20774 (April 18, 2000)]

Dear Docket Officer:

The American Red Cross (ARC or Red Cross) appreciates the opportunity to submit additional comments on the proposed rule regarding *Suitability Determination for Donors of Human Cellular and Tissue Based Products* (Donor Suitability proposal or proposal). This regulation outlines the Food and Drug Administration's (FDA) plans to require manufacturers of certain human cellular and tissue-based products to screen and test the donors of cells and tissue used in those products for risk factors for clinical evidence of relevant communicable disease agents and diseases.

As the provider of approximately twenty percent of the nation's supply of human tissue, ARC agrees with FDA's policy in issuing this regulation. We believe it will help advance the safety standards for the tissue products we provide. We look forward to the additional actions under FDA development including finalization of this regulation as well as the regulation to require registration and listing, and to the development of regulations for Current Good Tissue Practices.

Our main points are as follows:

97N-484S

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- ARC agrees that Xenotransplantation recipients should be deferred as tissue donors, but feels strongly that the only donors who need to be deferred are the recipients themselves. "Close contacts" do not need to be deferred.

- ARC believes that our current methods for screening for potential transmission of Creutzfeldt Jacob Disease meet the proposal's requirements. We also recommend consideration of steps to promote the use of other replacement tissue, (e.g. pericardium, or fascia lata) as an alternative to dura mater, as an acceptable method for helping advance the safety of tissue products.

- By failing to directly subject any element of the tissue banking process, (e.g. tissue procurement firms, firms that obtain Med/Sex/Soc history) to FDA inspection and the regulation's requirements, the rule's effectiveness in enhancing safety standards is seriously compromised. ARC urges FDA to incorporate coverage of all tissue banking activities directly into the scope of the regulation (Section 1271.1(b)). By failing to include many firms which actually perform a significant process (e.g. screening or procurement), the foundation of this regulation's approach to improving safety, FDA sets up a two tier safety measure: those who are directly subject to FDA inspection, versus those who are not.

- The above views also pertain to screening donors of human cellular products.

Thank you for the opportunity to provide additional public comments. If you have any questions, please contact Anita Ducca, Director, Regulatory Relations at 703-312-5601.

Sincerely,

Glenn M. Mattei, Esq.
Interim Vice President
Quality Assurance/
Regulatory Affairs

Attachments

Comments by The American Red Cross
On the
Suitability Determination for Donors of Human Cellular and Tissue Based Products
[Docket No. 97N-484S, 65 FR 20774 (April 18, 2000)]

The American Red Cross, through its National Tissue Services, provides approximately twenty percent of the nation's tissue needs for transplantation. ARC supplies cardiovascular, musculoskeletal, as well as skin, allograft tissue to physicians and dentists for patient treatment. ARC thus has an interest in consistent regulation of human tissues intended for transplantation. ARC is committed to working with FDA in its efforts to develop a regulatory program for human cellular and tissue-based products.

As ARC noted in our previous letter providing comments on this proposal, (December 27, 1999), we generally support this regulation. It is clear that FDA has thoroughly considered the appropriate issues. However, since that time, additional information has come to our attention that we believe should be added to the public record. We hope that this additional information and views will prove beneficial in preparing a final regulation regarding *Suitability Determination for Donors of Human Cellular and Tissue Based Products* (Donor Suitability regulation).

Xenotransplantation

FDA has proposed to defer potential tissue donors who have been Xenotransplantation recipients or their "close contacts". Page 52704 of the preamble states:

> FDA is proposing to define "Xenotransplantation" in Sec. 1271.3(aa) as any procedure that involves the use of live cells, tissues, or organs from a nonhuman animal source, transplanted or implanted into a human, or used for ex vivo contact with human body fluids, cells, tissues, or organs that are subsequently given to a human recipient. Nonliving biological products or materials from animals, such as porcine heart valves, porcine insulin, and bovine serum albumin, have been used clinically for decades and would not be considered Xenotransplantation products for purposes of these regulations. "Close contacts" of a xenotransplant recipient would be defined in proposed Sec. 1271.3(bb) as household members and others with whom the recipient participates in activities that could result in exchanges of bodily fluids.

ARC is concerned primarily because the definitions of these terms lack precision and therefore would be difficult to implement effectively. Although we agree that Xenotransplantation recipients should be deferred, we also believe that:

- The only donors who need to be deferred are those who have received the transplant itself.
- Additional screening questions for the donor's families should be limited to asking whether the potential donor has received a transplant from either a human or an animal source.
- The terms used to define which types of transplantations and/or exposure, and reasons for deferral are unfamiliar to the public. They would require substantial clarification before the regulation could be implemented.
- Similarly, the term "close contact" lacks clarity and even after careful reevaluation, it is unlikely FDA could reach a definition that could be implemented appropriately.
- The majority of the public is not familiar with Xenotransplantation, thus, there is likely to be confusion, since almost all of the potential donors will not have been affected even if families may think they have been.

ARC disagrees with the need to defer donors who are "close contacts" of a Xenotransplantation donor. We do not believe there is justification for deferral of other donors such as those in the same household, or in "close contact" with Xenotransplantation recipients. The potential tissue donor who has received a Xenotransplantation is iatrogenically immunocompromised as an element of the treatment necessary for the patient to tolerate the graft. This treatment puts the potential tissue donor/xenotransplant recipient at risk for such infections. However, to date there have been no reports of spread of zoonoses to "close contacts" or household members. Thus, we do not agree that "close contacts" should be deferred.

The definition of the term "close contacts" in section 1271.3(bb) is particularly troublesome:

> *close contact* means household members and others with whom the recipient participates in activities that could result in exchanges of bodily fluids.

This interpretation gives rise to numerous questions about the meaning of the term "close contact" and of the terms defining it. For example, transmission of certain diseases can occur by the exchange of body fluid during sexual contact, but the term "activities" used in the definition appears to be much broader. However, there is no further clarification of the term "activities" in the regulation. The phrase

"household members and others" is similarly ambiguous. Does this include visiting relatives and friends? If so, is there a time frame for how long the visit must last to be exposed?

FDA has recently encountered similar concerns expressed while considering potential policies regarding Xenotransplantation and blood donation. The term *close contact* was considered at length during FDA advisory committee meetings deliberating the draft *"Guidance for Industry: Precautionary Measures to reduce the Possible Risk of Transmission of Zoonosese by Blood and Blood Products From Xenotransplantation Product Recipients and Their Contacts"*. These meetings included the January 13, 2000 meeting of the Subcommittee on Xenotransplantation (Subcommittee) of the Biological Response Modifiers Advisory Committee and at the March 16 and 17, 2000 meeting of the Blood Products Advisory Committee.

At the Subcommittee meeting, there was a recommendation to change the term "close contact" to "intimate contact". Red Cross agrees that this is an improvement, in that "intimate contact" more directly addresses exposures of potential concern, and it could be defined with greater clarity. However, it should be noted that both advisory committees were concerned about the lack of definitive evidence demonstrating a risk of disease transmission by way of a Xenotransplant recipient or contact's blood donation. We suggest that the same holds true for tissue transplants.

ARC also believes that there is a more efficient alternative method to screen Xenotransplantation recipients. ARC recommends revising the Agency's guidelines on Xenotransplantation, including the Infectious Disease Issues in Xenotransplantation, and guidances related to clinical protocols, to include requirements to counsel patients and their families about their options for becoming tissue donors. Thus, the duty to inform the xenotransplant recipient and his or her family could more easily be accomplished during the informed consent process at the transplant center.

However, other issues remain. Specifically, we still believe that there is considerable ambiguity in the term "contact". Relatives of potential tissue donors participating in the screening process are unlikely to have sufficient knowledge of the donor's life style to be able to answer questions about whether their loved one had an intimate contact with a Xenotransplant recipient.

ARC voiced additional concerns when we testified before the Xenotransplantation Subcommittee.[1] ARC stated that criteria and definitions used for deferral policies needed further refinement before they could be put to practical use:

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[1] Attachment 2 contains ARC's at the January 13, 2000 Subcommittee Meeting.

> There is also a need for better definitions of *in vivo* vs. *ex vivo* exposure, particularly as it may apply to such potential blood donors as laboratory personnel. Similarly, this concern applies to animal workers, Veterinarians, veterinary staff, zoo workers, and others who may come in contact with animals alive or freshly killed such as farmers or meat slaughtering or packing staff. This could disqualify a very significant percentage of the donor population.

This same concern holds true for the proposed tissue donor regulation and specifically, the definition of Xenotransplantation contained in section 1271.3(aa):

> Xenotransplantation means any procedure that involves the use of live cells, tissues or organs from a nonhuman animal source, transplanted or implanted into a human, or used for ex vivo contact with human body fluids, cells, tissues or organs that are subsequently given to a human recipient.

Since there is no further clarification for the terms "live cells" and "ex vivo" it is uncertain whether an adequate set of tissue screening criteria can be developed, and it is very certain that different procurement firms will apply these requirements in an inconsistent fashion. Moreover, concerns about accurately determining the suitability of a blood donor are magnified when screening potential tissue donors, since the screening for these criteria would be done with families of the donors, who are far less likely to be able to accurately answer questions regarding the donor's medical history.

At most, there have been a few hundred total xenotransplant procedures performed since such treatments were initiated, so that the possibility of encountering a xeontransplantaiton recipient or a "close contact" is extremely remote. Yet the chance of a tissue donor deferral is likely to increase if this requirement is established as written either due to uncertainty on the part of the families providing screening information or to confusion about interpreting the regulation's requirements. ARC encourages FDA to recognize that unnecessary or unproductive screening criteria leads to a potentially far more serious health risk, that is, additional deferrals may reduce the availability of tissue when needed for medical treatments.

ARC believes that screening for Xenotransplantation recipients should be limited to a simplified question for the donor's family. That is, modify the current question to

ask if the donor has received a transplantation, and whether it has been from a human or an animal source. If the family answers positively, that donor would be deferred. Otherwise, the donor should be acceptable.[2]

Creutzfeldt Jacob Disease (CJD)

FDA has indicated that tissue facilities should also perform screening for transmissible spongiform encepahlopathies including Creutzfeldt Jacob Disease (CJD). Red Cross has no objection to performing such screening and has attached the questions we ask potential donors' families that relate to this screening. (See Attachment 5). ARC trusts that these questions, plus the review of medical records also required by the proposal, will appropriately fulfill the regulation's requirements.

We are pointing this out to help clarify that FDA did not intend to include the blood donor screening and donor deferral policy described in the November 23, 1999 Guidance for Industry on *"Revised Precautionary Measures to Reduce the Possible Risk of Transmission of Creutzfeldt-Jacob Disease and New Variant Creutzfeldt-Jacob Disease (nvCJD) by Blood and Blood Products"*. This policy was not mentioned in the proposal and was not issued until after the tissue Donor Suitability proposal was published.

If FDA intended procurers of human tissue allograft to apply the policies contained in above guidance for blood donors, ARC believes that FDA should state this point directly and specifically in the proposal. Additionally, we urge inclusion of a full discussion of the benefits of the additional screening in the preamble, to enable the public commentors to evaluate its application to tissue donations.

ARC believes that our approach to avoiding the potential transmission of CJD is appropriate for the types of tissue products we procure and process. In addition to the questions and the review of the potential donor's medical history, we have deliberately chosen to avoid procurement of dura mater. The tissue we procure can be processed into such products as paericardium and facia lata which can serve as substitutes for dura mater transplants.

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[2] Also attached are the Testimony of the American Association of Blood Banks (AABB) at the January 13 Subcommittee meeting (Attachment 3), and ARC's written comments on the draft *"Guidance for Industry: Precautionary Measures to reduce the Possible Risk of Transmission of Zoonosese by Blood and Blood Products From Xenotransplantation Product Recipients and Their Contacts"*. (Attachment 4)

This approach, i.e., supplying a substitute product that is much less likely to transmit CJD, is another important means of helping to improve the safety of tissue products. Thus, we ask FDA to recognize that product substitution can be used to augment current procedures to help ensure product safety.

Facilities Subject to the Donor Suitability Regulation

As ARC noted in our previous comment letter, we are concerned about the inconsistent application of this regulation to all facilities that procure tissue. ARC wishes to reemphasize this point:

> ARC is troubled... it appears that the Agency does not plan to extend the registration and listing regulation to include registration of individuals performing procurements under contract, and we do not understand the justification for allowing some procurers to be subject to FDA rulemaking and inspection, while others are not.

This proposal, which depends on the registration and listing regulation to identify facilities subject to its requirements, likewise appears to apply only to manufacturers of tissue, and fails to mention those whose sole function is to procure tissue.

The proposed Donor Suitability regulation is designed to help ensure identification of appropriate donors prior to and during tissue procurement. This is accomplished through (1) questions asked of the potential donor's family, (2) review of the donor's medical records, and (3) obtaining the test sample from the potential donor, all primary safety steps conducted by the firm which procures the tissue. Thus, a regulation governing tissue donor selection ***is*** a regulation of procurers.

In some cases, these firms are also the manufacturer of the tissue after procurement, but in many cases, they do not. These steps can be performed by firms whose sole function is tissue procurement, not the manufacturing or processing. Failing to include these procurement firms in the rule's scope, creates a significant gap in the effectiveness of the regulation.

Yet, as we read the Establishment Registration and Listing proposed rule and the current tissue Donor Suitability proposal, FDA intends to subject only manufacturers to the regulation's requirements.[3] Independent tissue procurers would not be subject to the same oversight for compliance with the regulation, and they will not be subject to inspection by FDA.

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[3] *Establishment Registration and Listing for Manufacturers of Human Cellular and Tissue-Based Products.* (63 FR 26744, May 14, 1998)

Failing to directly subject all procurers to these donor-screening requirements, is an inappropriate regulatory approach. By way of analogy, the equivalent regulatory scheme for the anticipated Current Good Tissue Practices regulation (CGTPs) would be for FDA to issue the CGTPs, and state that tissue procurement firms are required to follow CGTPs, but avoid including all manufacturing firms.

However, the statement regarding scope of the regulation found in Section 1271.1(b)

> manufacturers of those products are required to comply with the... current good tissue practice procedures in subpart D...in addition to all other applicable regulations.

indicates that FDA does not intend to take such a clearly unworkable approach for CGTPs. They intend to place responsibility for following manufacturing safety standards directly with those firms which perform the manufacturing activities. ARC urges FDA to adopt the same policy for those who procure tissue. Specifically, FDA should state that all tissue procurement firms are directly subject to the Donor Suitability regulations. Once this policy is implemented, the Donor Suitability regulation will cover those firms which actually perform the steps required by the regulation.

Human Cellular Products

As FDA noted in the proposal, the regulation is intended to apply to donors of human cellular products as well as tissue products. ARC wishes to clarify that our comments also apply equivalently to suitability of donors of human cellular products.

Closing

Red Cross appreciates the additional opportunity to comment on the proposed rule. If you have any further questions on this letter, please contact Anita Ducca, Director, Regulatory Relations of Quality Assurance/Regulatory Affairs at (703) 312-5601.

TESTIMONY BY
Rebecca Haley, MD

ON BEHALF OF
THE AMERICAN RED CROSS

On FDA's Draft "Guidance for Industry: Precautionary Measures to Reduce the Possible Risk of Transmission of Zoonoses by Blood and Blood Products from Xenotransplantation Product Recipients and Their Contacts"

Docket No. 99D-5347

January 13, 2000

The American Red Cross is pleased to have the invitation to speak regarding the FDA's recommendations for the prevention of transmission of zoonotic pathogens from xenotransplantation recipients through blood transfusions. The American Red Cross collects over six million units of blood from volunteers each year in the United States. I am Rebecca Haley, Senior Medical Officer at Biomedical Headquarters responsible for the medical aspects of donor qualification.

ARC agrees that a deferral policy for Xenotransplantation is appropriate. We understand there is a theoretical risk of disease transmission from recipients of xenotransplants if they should become blood donors in the post-transplant period. Facilities performing xenotransplants are guided by Draft Public Health Service Guideline on Infectious Disease Issues in Xenotransplantation (1996) to include in their consent form for patients that they should no longer be blood donors. The current proposed donor questions assume that this guidance has not been followed. In addition, we are very concerned that the guidance, in its current form, needs considerable clarification and revision before it would be workable for the blood collection facilities. The guidance is quite expansive and includes a number of groups in the deferred donor category.

ARC believes that the only donors who need to be deferred are those receiving the transplantation itself. We do not believe there is justification for deferral of other donors such as those in the same household, or in "close contact" with Xenotransplantation recipients. The recipient is iatrogenically immunocompromised as an element of the treatment necessary for the patient to tolerate the graft. This treatment puts the recipient at risk for such infections. To date there have been no reports of spread of zoonoses to "close contacts" or household members.

Additional donor questions are unnecessary. The donor questions as suggested would not elicit the expected results since the concepts about xenotransplantation are not well known by the general public. We currently have a question that asks the donor if he/she has received a blood transfusion, an organ or tissue transplantation. We could include information in the "What You Must Know" section to point out that organ xenotransplants are appropriate for reporting in this section. This question could easily

apply to Xenotransplantation tissue, as well. If the donor answers affirmatively, the Health Historian can ask additional questions, separate from the questionnaire, about their transplantation experience and whether it involves animal tissue.

The terms used to define which types of transplantations and/or exposures are vague. Better definitions are needed as well as more examples. Deferral policies are based on criteria discussed in the guidance, yet those criteria are either not defined or only vaguely defined. These include such concepts as Xenotransplantation of *living vs. non-living* cells. FDA appears to allow those receiving "nonliving cells" to donate, but those who receive living ones may not. The guidance gives a few examples, but not a clear definition. Without clear definitions, collection staff will not be able to assess donors that answer affirmatively to a yes response by a donor. Thus, deferral policies are not clear for those receiving organ or tissue transplants not included as one of the guidance examples. There is also a need for better definitions of *in vivo* vs. *ex vivo* exposure, particularly as it may apply to such potential blood donors as laboratory personnel. Similarly, this concern applies to animal workers, Veterinarians, veterinary staff, zoo workers, and others who may come in contact with animals alive or freshly killed such as farmers or meat slaughtering or packing staff. This could disqualify a very significant percentage of the donor population.

The majority of the public is not familiar with Xenotransplantation or disease transmission by this route. Thus, there is likely to be a significant amount of confusion at donor collection sites and a lack of consistency in implementation. The suggested questions talk about medical situations that are very unfamiliar to most Americans. If such a line of questioning is pursued and the potential donor does not know what you are talking about, can an "I don't know" suffice for a "No" answer? Section III.A.5. allows discretion on the part of the medical director to permit donation if "the nature of the exposure to the contact is unlikely to result in the exchange of bodily fluids and the medical director concurs that deferral is not warranted." The medical director typically accepts or defers donors on evidence of risk. For well, non-immunocompromised contacts, there is no medical evidence for deferral. When we defer donors they expect a factual reason for the deferral. We already push the limit of tolerance of our donors with the current questions with very long and arbitrary time frames concerning deferral events. Now if we implement another set of "have you ever " questions with vague indication, it will test the patience of most and enrage other donors. These questions engender an adversarial tone in the donor interview that discourages donors from returning. As we discuss these matters most of the United States is on appeal for blood donors and elective surgeries are being cancelled. The potential for harm from a lack of blood donors is very real and has often been highlighted by the Secretary of Health and Human Services, Dr. David Satcher, as a serious concern for medicine in the United States.

In the case of plasma derivatives, current manufacturing methods are likely to mitigate many of the potential infectious risks, particularly for enveloped agents such as retroviruses. Withdrawals of plasma derivatives have caused serious supply problems in the recent past. This would be likely to happen again with definite potential for harm where the theoretical exposure to zoonoses does not have a definable risk.

AMERICAN
ASSOCIATION
OF BLOOD BANKS

STATEMENT OF THE AMERICAN ASSOCIATION OF BLOOD BANKS

BEFORE THE XENOTRANSPLANTATION SUBCOMMITE
Of the
Biological Response Modifiers Advisory Committee

January 13, 2000

Presented by Kay R. Gregory, MS, MT(ASCP)SBB
Director Regulatory Affairs

The American Association of Blood Banks (AABB) is the professional society for over 9,000 individuals involved in blood banking and transfusion medicine and represents roughly 2,200 institutional members, including community and Red Cross blood collection centers, hospital based blood banks, and transfusion services as they collect, process, distribute, and transfuse blood and blood components and hematopoietic stem cells. Our members are responsible for virtually all of the blood collected and more than 80 percent of the blood transfused in this country. For over 50 years, the AABB's highest priority has been to maintain and enhance both the safety and availability of the nation's blood supply. The Association operates a wide array of programs to meet this safety and availability priority and is proud to have played a key role in ensuring that the nation's blood supply is safer today than ever before.

The AABB appreciates this opportunity to comment on the draft guidance document addressing the potential deferral of donors due to precautionary measures to reduce the possible risk of transmission of Zoonose by blood and blood products from xenotransplantation product recipients and their contacts.

Xenotransplantation is an exciting emerging technology that holds future promise for ameliorating the shortage of donor tissues for the treatment of serious, disabling diseases. Recognizing the important potential risk of transmitting zoonotic pathogens to patients by this route, we agree that xenotransplant recipients are unacceptable donors of allogeneic blood and tissue. Parenthetically, because of donor restrictions regarding medication use and general health, virtually no xenotransplant recipient would be a qualified blood donor at this time. The theoretical risk was well articulated in August 1996 in the *Draft Public Health Service (PHS) Guideline on Infectious Disease Issues in Xenotransplantation* which states "Consent forms should state clearly that xenograft recipients should never, subsequent to receiving the transplant, donate Whole Blood, blood components, Source Plasma, Source Leukocytes, tissues, breast milk, ova, sperm, or any other body parts for in humans." The language appropriately recognizes the primary responsibility of the transplant community for the apprisal of their patients about zoonotic risks.

We believe strongly that this aspect of the HHS guidance should be implemented. Even pending formal implementation of such guidance, FDA can insist on inclusion of such information in consent procedures as a condition for acceptance of clinical protocols for xenotransplantation. The FDA can also require that all current surviving xenotransplant recipients be contacted to assure that they understand they must not donate blood or tissue. Blood collection facilities can reinforce the prohibition on donation by including the xenotransplant exclusion in the written materials blood donors are required to study before

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each donation. This avoids addition of time consuming, confusing and unvalidated questions to the donor interview.

That said, several aspects of the draft guidance are problematic. Donor screening is already lengthy and complex. We have provided committee members with a copy of the most recents AABB Uniform Donor History (sanctioned by FDA) which contains 32 separate elements including inquiries into highly sensitive personal areas of sexual activity and drug use and references to such rare diseases as babesiosis and the transmissible spongiform encephalopathies. FDA proposes to add three complex questions to this process. REDS investigators (Williams et al. JAMA. 1997) have reported that 1.8% of anonymously surveyed accepted blood donors admit to deferrable risks, and we suspect that a substantial proportion of that is due to the length and complexity of the donor interview. The proposed donor questions in this draft are far too arcane to add to the current screening process and will produce donor confusion. In fact, the individuals that I asked to review these questions unanimously agreed that there were not understandable. This will result in unneeded deferrals at a time of borderline blood supply adequacy and declining donations. At a minimum, additional questions proposed by FDA for the reduction of *de minimis* risk must be validated for sensitivity, specificity and positive predictive value before being added to what is already referred to as the "donor interrogation" process. Further antagonism of the altruistic blood donor is unwarranted by current data.

A related concern is that increasing the complexity of the donor screening process for marginal theoretical risks may detract from its efficacy for documented risks like traditional viral transfusion associated infections and malaria. The result is then a paradoxical decrease in transfusion safety.

The requirement to defer as blood donors "sexual partner(s), any member of your household, or any other close contact" is ambiguous (lacking concise definition of household and other close contact). More important, this requirement for deferral is unsupported by any evidence of transmission of potential or unrecognized pathogens to such contacts after xenotransplantation. It is a slippery slope from such donor deferrals to disqualification of large populations with significant occupational animal exposures such as abattoir workers, farmers, veterinarians, and medical researchers working with large animal models. We suggest that a risk assessment be undertaken among those with close contact to the relevant species for evidence of transfusable disease associations that would support zoonotic transmission of disease causing organisms. Given the small numbers of xenotransplants currently being performed and the potentially large populations with contact to nonhuman primates and swine, these epidemiological studies can be carried out long before xenotransplantation becomes prevalent.

In summary:

- We accept the necessity to defer recipients of xenotransplants but respectfully suggest that the transplant programs have primary responsibility to initiate this process as part of the consent process. Blood collection facilities can reinforce this with written information.

- We suggest that the addition of unvalidated donor interrogation questions for the theoretical risks of xenotransplantation may, at worst, paradoxically increase other risks of transfusion, and at best will contract further an already shrinking donor base.

- Deferral for contact with xenotransplant recipients is unwarranted at present and the risk of such contact is amenable to study in populations with occupational exposure to the relevant species

American Red Cross

National Headquarters

March 24, 2000

Kathryn C. Zoon, Ph.D.
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RE: Guidance for Industry: Precautionary Measures to Reduce the Possible Risk of Transmission of Zoonoses by Blood and Blood Products From Xenotransplantation Product Recipients and Their Contacts - [Docket No. 99D-5347, 64 Fed. Reg. 73562 (Dec. 30, 1999)]

Dear Dr. Zoon:

The American Red Cross (ARC/Red Cross) wishes to thank the Food and Drug Administration (FDA) for the opportunity to comment on the draft guidance regarding *Precautionary Measures to Reduce the Possible Risk of Transmission of Zoonoses by Blood and Blood Products From Xenotransplantation Product Recipients and Their Contacts.*

ARC is the largest supplier of blood products and one of the largest providers of blood services in the United States. Each year, the Red Cross collects, processes, and distributes approximately six million units of whole blood, representing half the nation's blood supply. The blood donated by Red Cross volunteers is also recovered and processed or fractionated into plasma derivatives. After collection and recovery, these plasma units are transported to several vendors with whom we have established contracts to manufacture antihemophilic factor, intravenous immune globulin, albumin and solvent-detergent treated products under the FDA licenses of those companies. These plasma products are distributed under the American Red Cross label to hospitals, hemophilia treatment centers, and other providers.

ARC will be subject to the guidance as it applies to both the collection of blood and to product quarantine and withdrawal recommendations. Thus, we have outlined our views on the draft guidance below.

I. Summary of ARC's Views

On January 13, 2000 ARC and several other organizations involved in the collection, processing or use of blood and plasma derivative products testified before the Xenotransplantation Subcommittee of the Biological Response Modifiers Advisory Committee (Subcommittee) with regard to the proposed draft guidance. ARC would first like to restate its views on the draft guidance as articulated at that meeting:

- ARC believes that a deferral policy for Xenotransplantation patients is appropriate.
- The only donors who need to be deferred are those receiving the transplant itself.
- Additional donor questions are unnecessary.
- The terms used to define which types of transplantations and/or exposure are so rarely used and unfamiliar to the public that they would require substantial revision and/or clarification before the guidance could be implemented.
- The majority of the public is not familiar with Xenotransplantation, thus there is likely to be confusion and lack of intended effect, since almost all of the potential donors who may think they are affected will not have been.

II. Donor Questions (Draft Guidance - Section III.A.4.)

ARC is particularly concerned with the addition of three new questions to an already overly burdensome donor questionnaire. While well intended, Red Cross believes that reliable implementation of these questions would be difficult, if not impossible, due to their lack of clarity. Many donors already regard the numerous existing questions on ARC's blood donor questionnaire as overly intrusive. Donors may regard the inclusion of these questions as adding a delay in the donation process, rather than as contribution to public health or safety.

The terms "close contact" used in question 4.a. and 4.b. and the term "contact" used in question 4.c. are illustrative of this concern. For example:

- The lack of definition of "close contact" and "contact" will lead to varying interpretations and therefore inconsistent application of the questions.
- Without a clear definition, donors may require extensive clarification while preparing to donate at the blood collection center, requiring additional time to complete the donor screening process. The recommendations of the subcommittee were to include only intimate contacts of Xenotransplant recipients. This term is more easily definable, and perhaps more appropriate.
- Even if better definitions exist, it is likely that many donors will not know whether the contact is a Xenotransplant recipient or not.

At the Subcommittee meeting, there was a vote to change the term "close contact" to "intimate contact". Red Cross agrees that this is an improvement, in that "intimate contact" more directly addresses exposures of potential concern, and it could be defined with greater clarity. We hope that the duty to inform Xenotransplant recipients and "intimate contacts" will rest with the informed consent process at the transplant center as suggested by the Subcommittee. More importantly, ARC agrees with the concerns expressed at the Subcommittee meeting that there is a greater risk to public health by the potential for compromising the availability of the blood supply. Adding further time to the already lengthy donation process may discourage donors who already object to the process' length. They may choose to donate less frequently or avoid donation all together.

III. Alternative Approaches

As ARC and others mentioned during the Subcommittee meeting, we believe that there are alternative, and potentially far more effective, methods to help mitigate the risk of potential transmission of disease through Xenotransplantation. Specifically, at the time of the transplantation, the investigators conducting the transplantation could counsel recipients and their families regarding their blood donation options.

The investigators will have conducted extensive health assessments and health history evaluations of these patients, and may even interact with their families. Thus, their direct patient interaction, and the investigator's greater familiarity with Xenotransplantation's overall risks, renders this approach a far more effective way to minimize the risks of disease transmission.

We believe such steps, separate from the donation process, will far more efficiently reach the very few Xenotransplantation recipients and their families, estimated at no more than about 50 per year, than attempting to screen the 12,000,000 or more blood donors each year.

IV. Blood Product Quarantines and Withdrawals (Draft Guidance - Section III.B)

Our concerns for the blood product Quarantine and Withdrawal policies described in Sections III.B.1, III.B.2 and III.B.3 parallel our concerns about the donor deferral policies. Specifically, additional withdrawal policies will require notification to consignees, which will unnecessarily worry recipients of products from such donors and raise questions about the theoretical risk and harm to recipients. The blood industry will be at a loss to provide such guidance. In addition, when the risks of disease transmission are theoretical at best, there is a serious consideration that the policies may do more harm than good by reducing the availability of the blood supply. Even if the concern for the supply was lessened, existing manufacturing methods, and efficient viral inactivation procedures are likely to eliminate many of the potential infectious risks, especially for plasma derivative products.

Red Cross encourages FDA to reevaluate these withdrawal policies, and consider rescinding them for all circumstances, except where it is found that the donor him/herself is a Xenotransplantation recipient.

V. Providing Electronic Information on Xenotransplantation Recipients to Blood Collection Centers

During the Subcommittee meeting, it was suggested that FDA provide blood centers with a computerized list of Xenotransplantation recipients. The idea that as donors enter the collection site, they could be checked against the list to ensure they are not Xenotransplantation recipient. On the blood center side, we have the technological capacity and privacy protection processes in place to keep the list confidential if the FDA and Xenotransplant recipients choose this path. However, there are other considerations.

One is the additional time and extensive procedures for name verification that would be added to the donation process to work with such lists. Moreover, having the list will likely result in more unnecessary deferrals should any question regarding the accuracy of name matching occur.

More importantly, is the concern for confidentiality of the Xenotransplant recipient's medical records. At a minimum, permission will be needed from Xenotransplantation recipients for including their names on computerized lists that would then be distributed to blood centers nationally.

VI. Revisions Proposed to BPAC March 17, 2000

During the Blood Products Advisory Committee (BPAC) meeting on March 17, FDA summarized the discussion and vote at the Xenotransplantation Subcommittee meeting. FDA also presented several revisions to the Guidance, including a revision to the previous questions and suggested language to be added to donor educational materials. ARC has reviewed these materials and believes that the revisions as proposed do not fully address the concerns we have expressed above and in our testimony on January 13 about the Draft Guidance. (see Attachment)

In particular, ARC does not believe that additional questions are necessary, and the revisions do not alleviate several additional comments describe by the ARC and others. Specifically, the additional questions will slow the donation process. Further, without validation, there is no assurance the revised version will generate accurate responses.

ARC continues to urge FDA to consider the alternative of discussing implications for blood donation with Xenotransplantation recipients and their relatives at the time of transplant.

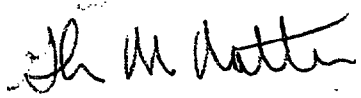
VII. Revision of the Draft Guidance

Based on the information discussed at both the Subcommittee meeting and the BPAC meeting, as well as public comment likely to be received on this topic, it is likely that FDA will revise the draft guidance prior to finalization. We believe that the Agency has, so far, very responsibly managed this issue, both by accessing the appropriate advisory Committees and by soliciting public comments. In particular, we appreciate the opportunity to file written comments with FDA after the BPAC meeting so that an assessment of the additional work performed after the Subcommittee meeting might be possible.

However, we anticipate considerable changes as a result of the Committee meetings and the public comments submitted to date. Therefore, we wish to be able to continue our participation as the Agency's policies unfold in this area. ARC requests that FDA reissue the guidance as a revised draft, prior to issuing a final version, so that the public may file comments on what is likely to be a substantially different guidance.

If there are any questions regarding this letter, please contact Anita Ducca, Director, Regulatory Relations at 703-312-5601.

Sincerely,



Glenn M. Mattei, Esq.
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Attachment

ARCTS Tissue Donor Questions Relating to CJD[1]

21. Suffer from any type of neurologic or brain disease such as Alzheimer's, seizures, periods of confusion or recent memory loss, history of brain tumor? Has the potential donor or any of the donor's blood relatives had Creutzfeldt-Jakob Disease, or been told they or their family were at increased risk for Creutzfeldt-Jakob Disease (CJD)?

25. Ever been given human pituitary derived growth hormone?

[1] Obtained from the *ARCTS Cadaveric Tissue Donor Medical History Interview.*

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